Psychological Factors Predict an Unfavorable Pain Trajectory after Hysterectomy: a prospective cohort study on chronic post-surgical pain

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Abstract

Chronic post-surgical pain (CPSP) is a well-recognized potential complication with negative personal, social and healthcare consequences. However, limited data exists on CPSP and on the course of pain over time after hysterectomy. Using data from a prospective cohort study on a consecutive sample assessed at 4 time points, pre-surgery (T1), 48 hours (T2), 4 months (T3), and 5 years post-surgery (T4), we sought to examine women's post-surgical pain trajectories using assessments of pain at T3 and T4. Additionally, this study aimed to investigate pre-surgical and post-surgical risk factors associated with an unfavourable pain trajectory (PT). Based on pain data collected at T3 and T4, three distinct trajectories of post-surgical pain (PSP) emerged: no CPSP (PT1;n=88), prolonged PSP (PT2;n=53) and CPSP (PT3;n=29). Moreover, reported CPSP prevalence at 5 years was 17.1%. Multinomial logistic regression models controlling for age, pre-surgical pain and type of hysterectomy tested for baseline and acute post-surgical predictive variables. Membership in PT2 and PT3 was predicted by pre-surgical anxiety (OR=1.131, p=0.015; OR=1.175, p=0.009, respectively), emotional representation of the surgical disease (OR=1.155, p=0.034; OR=1.213, p=0.020, respectively) and pain catastrophizing (OR=1.079, p=0.043; OR=1.143, p=0.001, respectively). Furthermore, acute post-surgical pain intensity and frequency determined membership of women in PT3 (OR=1.211, p=0.033; OR=3.000, p=0.029, respectively), and post-surgical anxiety (OR=1.182, p=0.026) also played a key predictive role. This study identified factors that can be easily screened before and after surgery, and are amenable to change through carefully designed timely and tailored interventions for women at risk of an unfavorable post-surgical pain trajectory post-hysterectomy.

Keywords: hysterectomy; post-surgical pain trajectory; chronic post-surgical pain; prospective cohort study; psychological factors; acute post-surgical pain

1. INTRODUCTION

Chronic pain after surgery is a well-recognized potential complication, being acknowledged as a major clinical problem with significant individual, social and healthcare costs [52,56, 60]. It is a serious public health issue, since surgeries are widely performed, increasing the numbers of those at risk [13,49,56]. Indeed, the current version of the International Classification of Diseases (ICD-11) for chronic pain categorization already proposes chronic post-surgical pain (CPSP) as a new distinct entity among seven groups of chronic pain disorders [103].

CPSP was first mentioned in 1998 [26], being highlighted that 22.5% of patients attending 10 pain clinics pointed surgery as the cause for chronic pain. Despite improvements in knowledge regarding epidemiology and CPSP burden, its underlying mechanisms are not fully understood [48,105]. However, evidence suggests that CPSP development is multifactorial, rooted in a dynamic and complex interplay amongst biological, psychosocial and environmental factors [23,49]. To increase knowledge, research has focused increasingly on understanding risk factors, in hopes of finding new ways to treat and ultimately prevent CPSP from occurring.

Risk factors are often conceptualized into pre-surgical, intra-surgical and post-surgical, embracing variables such as age, surgery type, previous pain and acute post-surgical pain [52,53,60,63,74]. Psychological factors are well-documented predictors for CPSP across different surgeries [2,15,41,44,62,77], including anxiety [59,62,100], depression [110], pain catastrophizing [28,51,57,59,100] and optimism [40,83]. In an attempt to systematize information, VanDenKerkhof et al [105] proposed a framework wherein risk factors are organized into five domains: demographic, pain, clinical, surgery-related, and psychological.

Hysterectomy is the most common gynecologic surgery performed in women in Western countries [86,99]. In a review including 11 hysterectomy studies, with follow-up times up to 2 years, CPSP was reported by 5-32% of women [8]. Subsequent studies kept diverging on prevalence rates. These differences were likely due to distinct CPSP definitions, heterogeneity of measurement and differences in follow-up times; some were 3 [101], 4 [6,68,80], 6 months [81,104], 1 [7,68,101] or 2 years [68]. Simultaneously, risk factors that have been most highlighted were age [68,80], pre-surgical pain [7,68,101,104], other pain problems [6,7,68,80] and psychological factors [68,80,101,104]. Within the latter, there was some heterogeneity due to different measures used. Furthermore, acute post-surgical pain intensity was more strongly related with CPSP in some hysterectomy studies [6,101,104] than in others [68,80], with one of the studies proposing post-surgical pain frequency as a better predictor than intensity [80].

Whilst the incidence and risk factors for CPSP have been widely explored, knowledge on the course of post-surgical pain over time is limited. Identifying patients who are at risk of an unfavorable pain trajectory, culminating in CPSP, provides a unique opportunity to investigate the transition from acute to chronic pain and is critical to developing a more comprehensive understanding of CPSP and establishing potential targets for psychosocial and clinical interventions.

Therefore, the aims of this study were: (1) to examine post-surgical pain trajectory up to 5 years after hysterectomy; (2) to investigate baseline predictors of different pain trajectories; and (3) to further explore the added predictive value of acute post-surgical factors in pain chronification.

2. METHODS

2.1. Participants and Procedure

This study was conducted in a central hospital in northern Portugal and approval was granted by the Hospital Ethics Committee. This was a prospective cohort study with longitudinal assessments at 4 time points: 24 hours before surgery (T1), 48 hours (T2), 4 months (T3) and 5 years (T4) after surgery. Assessments were performed between March 2009 and January 2015. A consecutive sample of 203 women, undergoing hysterectomy due to benign causes, was invited to participate in the study and all provided written informed consent. Inclusion criteria were age between 18 and 80 years, and the ability to understand consent procedures and questionnaire materials. Exclusion criteria were the presence of psychiatric or neurologic pathology (e.g. dementia) and undergoing hysterectomy due to malign conditions or in emergency setting. Time 1 and T2 assessments took place in hospital, T3 and T4 follow-up assessment were conducted by telephone interview. Inclusion in each assessment point and the reasons for loss to T2, T3 and T4 are shown in a flowchart (**Figure 1**). The final sample is comprised of 170 women (retention rate: 83.7%; age: *M*=50.8; *SD*=9.03; minimum=35; maximum=76) with assessments performed at T1, T2, T3 and T4. The 33 women lost to follow-up, from T1 to T4, did not differ significantly from the women evaluated over 5 years in terms of baseline demographic, psychological and clinical characteristics, namely on surgical, anesthetic and analgesic issues.

Data related to this sample have been described in four previous publications reporting predictors of acute post-surgical pain [76,77], predictors of rescue analgesia administration [79] and predictors of persistent post-surgical pain 4 months after hysterectomy [80]. The present work is the first to report the long-term outcomes in this sample, 5 years post-hysterectomy, including the four assessment points.

2.2. Data Collection

2.2.1. Pre-surgical assessment – 24 hours before surgery (T1)

At hospital admission, and in order to get a baseline evaluation of women, the Portuguese versions of the following questionnaires were administered, in a face to face interview, by a trained health psychologist.

2.2.1.1. Socio-Demographic Questionnaire: included questions on age, height, weight, education, residence, marital status, professional status, household and parity.

2.2.1.2. Clinical Questionnaire: enquired about previous pain, either related to the cause of surgery or due to other causes, previous surgeries, menopause status, diagnosis/indication for hysterectomy and disease onset, uterus height and weight, as well as the use of psychotropic drugs (anxiolytics and anti-depressants).

2.2.1.3. The Brief Pain Inventory – short form (BPI-SF) [24]: employed among women reporting pre-surgical pain (related with the disease underlying the surgery). It measured: pain location in the body; pain intensity on an 11-point numerical rating scale (NRS; 0 represents "no pain" and 10 the "worst pain imaginable"); analgesic intake; perception of analgesic relief; and pain interference with daily life on an 11-point NRS (0 = "does not interfere" and 10 = "completely interferes") in distinct dimensions (general activity, mood, walking, work, relations with others, sleep and enjoyment of life). Higher scores represent higher levels of pain interference. In this study, the internal consistency reliability [27] for the pain interference subscale scores was high (α = 0.90).

2.2.1.4. The Hospital Anxiety and Depression Scale (HADS) [112**]:** comprised by two subscales used to measure anxiety and depression via 7 items each. Subscale scores range from 0 to 21 and result from the sum of each item (Likert scale ranging from 0 to 3). Higher scores correspond to higher levels of anxiety and depression. In the current sample, internal consistency reliability was adequate for both anxiety T1: α = 0.77; T2: α = 0.84) and depression (T1: α = 0.81).

2.2.1.5. The Surgical Fear Questionnaire (SFQ) [102**]:** used to evaluate specific surgical fears via 8 items aggregated in 2 subscales, "fear of immediate consequences of surgery" (α = 0.77; 4 items) and "fear of long-term consequences of surgery" (α = 0.75; 4 items). Each item score ranges from 0 to 10; item scores are summed to calculate each total subscale score. Subscale scores range between 0 and 40, with higher values indicating higher levels of fear.

2.2.1.6. The Revised Illness Perception Questionnaire (IPQ-R) [69]: employed to assess patient beliefs about the underlying disease that lead to surgery, is comprised by seven dimensions. In the current study, and with the aim of diminishing participant burden, a psychometrically shortened version [78,80] was used, with 3 items composing each one of the 7 subscales: “timeline acute/chronic” (α=0.79; e.g. “My illness will last for a long time”); “timeline cyclical” (α=0.74; e.g., “My symptoms come and go in cycles”); “consequences” (α=0.56; e.g., “The disease underlying surgery has major consequences on my life”); “personal control” (α=0.53; e.g., “I have the power to influence my illness”); “treatment control” (α=0.76; e.g., “Surgery can control my illness”); “illness coherence” (α=0.78; e.g., “My illness is a mystery for me”); “emotional representation” (α=0.88; e.g., “When I think about my illness I get upset”). “Consequences” and “personal control” were not included due to their low score reliability in this sample (α=0.56 and α=0.53, respectively). Each item is rated on a scale of 1-5 and to calculate each total subscale score, items are summed. Each subscale varies between 5 and 15, with high scores revealing less adaptive illness perceptions, with the exception of personal and treatment control subscales, which score inversely.

2.2.1.7. The Coping Strategies Questionnaire – Revised Form (CSQ-R) [88**]:** used to evaluate six pain coping strategies: pain catastrophizing” (5 items; α=0.88); “praying and hoping” (3 items; α=0.88); “ignoring pain” (5 items; α=0.92); “distraction/diverting attention” (5 items; α=0.77); “reinterpreting pain” (4 items; α=0.74); and “pain coping self-statements” (4 items; α=0.70). During pilot testing, subjects were often confused by the usual 7-point Likert-type scale. Therefore, a 5-point rating scale was used (1=never, 2=almost never, 3=sometimes, 4=almost always, and 5=always), which was shown to be more easily understood. The total subscale score was obtained by the sum of the item scores, with higher scores indicating greater use of the specific coping strategy.

2.2.1.6. ***Life Orientation Test – revised*** **(LOT-R) [9**3**]:** evaluated the personality trait optimism using 8 items. The total score ranges from 0 to 12 (α=0.95), with high values associated with more optimism.

2.2.2. Post-surgical assessment – 48 hours after surgery (T2)

Forty-eight hours after surgery, women were again assessed in a face-to-face interview by the same Psychologist who performed the baseline assessment in T1.

2.2.2.1. Acute post-surgical pain measurement

Worst and average level of acute pain intensity, within the first 48 hours after surgery, were assessed using an 11-point numerical rating scale (NRS from the BPI-SF described above) [24].

The post-surgical pain frequency assessment was performed using the frequency scale of the McGill Pain Questionnaire [67]. Pain could be defined either as constant (continuous, steady), intermittent (periodic, rhythmic) or brief (momentary, transient).

2.2.2.2. Post-surgical anxiety

Post-surgical anxiety was evaluated again at this time point using the HADS anxiety subscale [112] already described.

2.2.3. Post-surgical assessment – 4 months (T3) and 5 years after surgery (T4)

Four months and 5 years after surgery, telephone calls were made to every participant in order to check for the presence of pain. The question was: "Do you still have any pain that you could link to surgery or that you could relate to the surgical procedure?". This is an adaptation of the BPI-SF first question on pain prospection. If women answered no, those women were classified as cases without pain. Contrarily, if women answered yes, they were considered pain cases. For those women reporting pain, additional measures were employed, which focused on pain assessment:

2.2.3.1. The Brief Pain Inventory – short form (BPI-SF) [24]: as described above.

2.2.3.2. Pain frequency description: pain frequency could be described as constant, daily, several times a week but not daily, several times a month but not weekly, during sexual intercourse, by touch or lifting weight.

2.2.3.3. Neuropathic Pain Questionnaire (DN-4) [4]: previous research described CPSP as a potential neuropathic pain [49,52]. This instrument assesses pain characteristics/quality using 10 items. Seven of them refer to specific pain sensory descriptors, such as burning, pinpricking or numbness, and patients answer if their pain has those characteristics using a dichotomous response format (yes or no). The last three items result from the sensory examination of patients performed by a clinician. For the purpose of this study, only the first seven items were included [5]. Besides the information regarding pain quality, this questionnaire also provides information concerning the potential likelihood of neuropathic pain, corresponding to a cut-off of 3 (DN4≥3).

2.3. Surgical procedures, anesthetic and analgesic techniques

Clinical data related to the surgery, anesthesia and analgesia was collected from medical records.

Regarding surgical procedure, among the 170 women who underwent surgery, 122 (71.8%) were submitted to total abdominal hysterectomy, 31 (18.2%) to vaginal hysterectomy, 11 (6.5%) to total laparoscopic hysterectomy and 6 (3.5%) to laparoscopically assisted vaginal hysterectomy. In abdominal hysterectomy (n=122), a Pfannenstiel incision was performed in 102 women (83.6%), being established as the first choice, with a vertical infra-umbilical incision being performed in 20 women (16.4%), corresponding to cases wherein a previous vertical surgical scar was present.

Concomitant procedures, such as oophorectomy, ovarian cystectomy, salpingectomy, cystoscopy or vaginal repair, were also performed in a few patients. Moreover, uterus weight and height were also recorded.

Concerning the type of anesthesia, 51 (30.0%) patients had general anesthesia, 22 (12.9%) had locoregional and 97 (57.1%) were submitted to combined anesthesia (general + locoregional). ASA score (physical status classification of the American Society of Anesthesiologists) was recorded, including cases of ASA grade I (49, 28.8%), II (107, 62.9%) and III (14, 8.2%).

In what regards analgesic procedures, a post-surgical 48 hours standardized analgesia protocol was assigned to all patients. This protocol was established and supervised by the Acute Pain Service, prior to the transferring of patients to the infirmary.

Delivery of the analgesic protocol was either epidural or intravenous. The standardized epidural protocols could be: a) a continuous epidural infusion (DIB - delivered infusion balloon) with ropivacaine (0.1%) and fentanyl (3ug/ml), administrated to 105 (61.8%) women; or b) administration of an epidural morphine bolus (2-3 mg, 12/12h), assigned to 14 (8.2%) women. The intravenous protocol consisted in a continuous intravenous infusion (DIB) of tramadol (600 mg), metamizol (6 gr) and metoclopramide (60 mg) and was used with 51 (30.0%) patients.

Paracetamol (1 gr 6/6h) and non-steroidal anti-inflammatory drugs (NSAIDs - ketorolac 30 mg 12/12h or parecoxib 40 mg 12/12h) were always included as coadjuvant analgesics. In addition, all analgesic regimens included prokinetic treatment that was standardized to metoclopramide (10 mg i.v. 8/8h). In cases of moderate or severe acute post-surgical pain levels (numerical rating scale, NRS>3) rescue analgesia was prescribed beyond the standardized analgesic protocol. Due to the great variability in analgesics' protocol and dosages, no attempt was made to determine total equianalgesic medication dosages. Instead, it was recorded whether rescue analgesics were given to patients or not.

The use of psychotropic drugs (anxiolytics and anti-depressants) during hospital stay was detailed from hospital records.

2.4. Statistical Analyses

The primary outcome variable under study is post-surgical pain trajectory, corresponding to three possible pain trajectory groups: (1) No CPSP or Pain Trajectory 1 (PT1), comprised by women who did not report pain neither at 4 months nor at 5 years after surgery; (2) Prolonged PSP or Pain Trajectory 2 (PT2), including women who complained of pain 4 months after surgery, but not 5 years after; and (3) CPSP or Pain Trajectory 3 (PT3), comprising those women who reported pain both at 4 months and 5 years after hysterectomy. These groups were defined taking into account pain report [yes (presence) or no (absence)] 4 months and 5 years after hysterectomy (T3 and T4).

To compare the three groups on the variables under analysis, Chi-square or Fisher tests and One-way ANOVA statistical tests were computed. For the latter, in the case of significant results ($p < 0.05$), Bonferroni post-hoc tests were performed in order to further investigate between-group differences. These preliminary analyses were exploratory, and were performed to determine the predictor variables to include in the subsequent regression analyses.

Finally, a set of predictive multinomial logistic regression models were conducted to investigate risk factors associated with pain trajectory group membership. The socio-demographic, clinical and psychological variables selected for the regression analyses were those that distinguished pain trajectory groups in univariate analyses. Two structural models were developed: Model 1 (M1), investigating the role of baseline pre-surgical variables (T1), allowing for the establishment of a pre-surgical risk profile; and Model 2 (M2), aiming at further understanding the role of acute post-surgical factors, 48 hours after hysterectomy (T2). These basic structural models, include demographic (age) and clinical [pain-related (pre-surgical pain) and surgery-related (type of hysterectomy)] variables that significantly distinguished the groups in univariate analyses, in order to control these effects in group comparisons.

Considering the role of pre-surgical baseline predictors, and due to shared variance among the five psychological predictors (and consequent multicollinearity), which emerged as significant in the distinction of the three groups, three different sub-models were considered. The first model (M1A) focused on emotional variables (pre-surgical anxiety and fear), the second (M1B) centered on illness perceptions (emotional representation of the disease underlying surgery) and the third model (M1C) tested the role of pain coping strategies (pain catastrophizing).

Regarding acute post-surgical factors, two models were computed, both controlling for the same abovementioned demographic and clinical variables that were controlled for in pre-surgical models. Beyond these covariates, the first model (M2A) tested for the specific predictive role of acute post-surgical pain intensity and frequency. The second post-surgical model (M2B) was akin to the first though it had the addition of post-surgical anxiety.

Data were analyzed using the IBM SPSS Statistics version 24.0. Internal consistency of responses to the questionnaires was assessed using Cronbach's alpha [27]. Results were considered significant for *p*-values < 0.05. Effect size measures were interpreted considering the Cohen's [25] rule of thumb for eta squared (η^2): small effect size=0.02; medium effect size=0.13; large effect size=0.26; and Rea & Parker [85] for Cramer's Phi (φ) or Cramer's V for nominal data: negligible association: 0 and under 0.10; weak association: 0.10 and under 0.20; moderate association: 0.20 and under 0.40; relatively strong association: 0.40 and under 0.60; strong association: 0.60 and under 0.80; very strong association: 0.80 and under 1.00.

3. RESULTS

3.1. Pain Trajectory (PT) according to pain report 4 months (T3) and 5 years (T4) after hysterectomy

Table 1 presents the number of women within each pain trajectory group, according to the course of pain up to five years after surgery.

Considering Pain Trajectory, 88 (51.8%, PT1) women did not complain of pain at 4 months or 5 years after surgery. This was the largest group and was called "No Chronic Post-Surgical Pain". This pain trajectory is a typical, expected and desirable one in terms of healing and normal recovery. The second group was comprised of 53 (31.2%, PT2) women who complained of pain 4 months post-surgery, but at 5 years after surgery did not experience any related pain. This group was labelled "Prolonged Post-Surgical Pain". The third Pain Trajectory group (PT3) included 29 (17.1%) women who reported pain both at 4 months and 5 years following hysterectomy. As their pain persisted over time, this group was labelled "Chronic Post-Surgical Pain". All patients reporting pain at the 5-year follow-up also had reported pain at 4 months post-surgery. Patients not reporting pain at the 4-months follow-up also did not report pain 5 years later. Thus, there were no cases of "new pain" with a later onset beyond the 4-month follow-up timepoint.

3.2. Differences among Pain Trajectory (PT) groups on socio-demographic, clinical and psychological variables

Table 2 shows that before surgery, PT groups differed in age [p=.013; η^2 =.051, small effect size (ES)], with PT1 being older than PT2 (p=0.003). Concerning clinical measures, the groups were similar in terms of surgical disease onset, BMI (body mass index), previous surgical procedures or pre-surgical psychotropic use. Regarding pre-surgical pain, the three groups of women differed significantly on pre-surgical pain related to the condition underlying surgery (p=0.032; φ =.201, moderate association), but not on previous chronic pain due to other causes (see Table 2). Among the 3 empirically derived pain trajectory groups, and regarding psychological variables measured before surgery, there were significant differences in anxiety (p<0.001; η^2 =.094, small ES), surgical fear related to long-term consequences of surgery (p=0.022; η^2 =.045, small ES), emotional representation of surgical disease (p=0.001; η^2 =.081, small ES) and pain catastrophizing (p<0.001; η^2 =.090, small ES). For all these variables, higher values were associated with chronic pain groups membership in PT2 or PT3.

In terms of surgery, the PT groups could be distinguished based on the type of surgical approach (p=0.007; φ = .242, moderate association) and among those undergoing abdominal hysterectomy there were also differences across groups on the type of abdominal incision (p=0.003; φ =.260, moderate association). The PT2 and PT3 groups had more women undergoing abdominal hysterectomy and a pfannenstiel incision.

In the acute post-surgical period, 48 hours after surgery, the three PT groups of women showed differences in acute pain report, regarding worst (p<0.001; η^2 =.096, small ES) and average (p=0.001; η^2 =.086, small ES) pain intensity, pain frequency (p=0.001; φ =.286, moderate association) and post-surgical anxiety (p<0.001; η^2 =.109, small ES). These differences showed that the PT2 and PT3 groups scored more negatively on these variables.

3.3. Pain incidence, characteristics and perceived impact 5 years after hysterectomy

Among the 170 women who completed the four assessments, 29 (17.1%) revealed an unfavorable pain trajectory after hysterectomy, reporting pain both at 4 months and 5 years after surgery, therefore being considered CPSP cases (Table 3). From these 29 cases of CPSP, Table 3 highlights that in terms of pain frequency, the majority of women (44.8%) reported pain several times a week, with 24.2% of women perceiving pain on a daily basis and 20.7% complaining of pain only during sexual intercourse or by touch. Additionally, the mean of worst pain intensity was 3.17 (SD=1.61) and the mean average level of pain intensity was 1.89 (SD=0.88), on the 0-10 NRS. It was also shown that 34.5% of CPSP women rated their worst pain intensity above 3 (NRS>3), indicating moderate and/or severe pain levels. Table 3 also reveals that the pain sensory characteristics more often described by CPSP patients were feeling of pins and needles (51.7%) and numbness (31.0%). In terms of a potential neuropathic pain component of CPSP, five (17.2%) women presented a DN4 ≥ 3 value. Pain interference was reported in all domains, the most common being mood (57.1%), enjoyment of life (50.0%), general activity (42.9%), normal work (42.9%) and walking ability (28.6%). Nevertheless, mean values of pain interference were in the low to medium range.

3.4. Predictors of Post-Surgical Pain Trajectory

In order to identify the pre-surgical predictors of an unfavorable pain trajectory, three multinomial regression models were computed (Table 4), controlling for the demographic and clinical variables that distinguished the three groups: age, previous surgical pain, and type of hysterectomy. The first Model (M1A) further tested for the influence of psychological factors related to emotional distress, namely pre-surgical anxiety and surgical fear related to the long-term consequences of surgery. Table 4 shows that pre-surgical anxiety is a predictor of pain trajectory, being a determinant of group membership, with higher anxiety scores being associated with both the “Prolonged PSP group” (PT2; OR = 1.131, *p* = 0.015; for each unit increased in pre-surgical anxiety, the odds of being in the PT2 group is 1.131 times higher than those of being in the PT1 group) and the “CPSP group” (PT3; OR = 1.175, *p* = 0.009), when compared with the “No CPSP group” (PT1). All other variables were not significant. Table 4 also reveals results on the influence of psychological factors associated with illness perceptions (M1B) and pain coping strategies (M1C). Within M1B, emotional representation of the condition underlying surgery emerged as the only factor significantly associated with group membership, with high scores predicting PT2 (OR = 1.165, *p* = 0.018) and PT3 (OR = 1.246, *p* = 0.005) membership. Within M1C, pain catastrophizing was the only variable yielding a significant association with either membership in PT2 (OR = 1.079, p = 0.043) or PT3 (OR = 1.143, p = 0.001) groups. Concerning factors that could distinguish PT2 from PT3 membership, Table 4 indicates that the psychological construct *fear of long-term consequences of surgery* was the only significant predictor (OR = 1.078, *p* = 0.049).

In order to further explore the role of acute post-surgical variables in the development of an unfavorable pain trajectory, over and above demographic and clinical factors, two subsequent models were tested (see Table 5). The first model (M2A) revealed that acute post-surgical pain intensity and frequency determined inclusion of women in PT3 (OR = 1.211, *p* = 0.033 and OR = 3.000, *p* = 0.029, respectively). The second post-surgical model (Model 2B) added post-surgical anxiety to the variables of the previous model in order to test its predictive role. Subsequently, both acute post-surgical pain intensity and frequency ceased to be significant and post-surgical anxiety became the only variable predicting PT3 (CPSP) (OR = 1.182, *p* = 0.026). Age, previous pain and type of hysterectomy did not contribute to the prediction of an unfavorable pain trajectory in any of the models (see Tables 4 and 5).

4. DISCUSSION

This prospective cohort study followed women up to five years after hysterectomy and found that pre-surgical anxiety, emotional illness representations and pain catastrophizing were risk factors for post-surgical pain. Higher post-surgical anxiety, acute pain intensity and frequency increased the likelihood of a worst pain trajectory. These results are novel since there are no prospective studies on chronic post-surgical pain (CPSP) after hysterectomy with such a long follow-up and that consider the trajectory of pain over two long-term follow-up times (4 months and 5 years post-hysterectomy). This study also adds to previous findings regarding pain at 48 hours [76,77] and 4 months [80] post-surgery.

4.1. CPSP Prevalence after Hysterectomy

Almost half of women (48.2%) reported pain 4 months after hysterectomy. Five years later, 17.1% still complained of pain. Within hysterectomy studies, the longest follow-up period we are aware of (2 years), revealed a CPSP prevalence of 24.1% and 16% in abdominal and vaginal hysterectomy, respectively [68]. With a 1 year follow-up, Theunissen et al [101] reported a prevalence of 9%, though the criteria underlying CPSP definition was a cut-off level of 3 (NRS>3), indicative of moderate or severe pain intensity. A retrospective study [7] reported 31.9% prevalence and in a prospective study [6], 4 months post-surgery and using a different CPSP definition (pain with impact on daily living), the prevalence rate was 16.7%. Two other studies described a prevalence of 14% [104] and 26% [81], 6 months post-hysterectomy.

These figures clearly reveal large discrepancies in CPSP report, most likely due to the diverse range of follow-up times and CPSP definitions [49,70]. The relatively higher prevalence of CPSP found in our study may be due to not having included only those women reporting moderate to severe pain (NRS>3). On the other hand, our findings show that pain only interfered with the lives of some women and that interference was in the low to medium range.

4.2. Predictors of CPSP after Hysterectomy

4.2.1. Demographic and Clinical Factors

In contrast to earlier findings [6,7,68,80,98,101,104], age and pre-surgical pain did not predict CPSP. Studies that found such relationships had shorter follow-ups, from 4 months to 2 years. Consistent with previous results [3,6,7,98,101,104], hysterectomy type did not predict CPSP albeit this does not support our earlier findings [80], nor Montes et al [68] conclusions. These results were unexpected and suggest that the strength of association of demographic and clinical factors probably diminishes with time, as psychological factors play an increasingly greater role. A similar conclusion was drawn previously in a post-mastectomy study with a 3-year follow-up [2].

Acute post-surgical pain intensity is a well-established key predictive factor [13,14,53,56,62,63], including in hysterectomy CPSP studies [6,81,98,101,104]. Present results support this and further add post-surgical pain frequency, as previously found in this sample [77]. To our knowledge, only Fletcher et al [35] found pain frequency to be a CPSP predictor. These results highlight pain frequency as a new potential target in CPSP prevention. When adding post-surgical anxiety to the equation, both acute pain predictors ceased to be significant, which indicates both their shared variance and the unique contribution of post-surgical anxiety in the prediction of CPSP.

It is noteworthy that the acute post-surgical variables only predicted pain five years later. This suggests that to prevent long-term post-hysterectomy pain, women should be screened and targeted throughout the perioperative period, and not only before surgery. Baseline assessments are useful for medium and long-term pain prediction whereas acute post-surgical variables seem to better predict long-term chronic pain.

4.2.2. The key Role of Psychological Predictors

Pre-surgical anxiety and pain catastrophizing were predictive of an unfavorable post-surgical pain trajectory and CPSP, which corroborates previous findings [16,44,100]. Pre-surgical anxiety, already shown to be a predictor of CPSP 4 and 6 months [80,104] post-hysterectomy, is also predictive of CPSP 5 years later. Furthermore, pain catastrophizing, a well-established CPSP psychological risk factor [2,15,51,57,84], appears as a predictor for the first time in our hysterectomy studies [80].

Our results also confirm the important role of emotional representation of the surgical disease and of post-surgical anxiety [80]. Other studies have demonstrated the impact of cognitive and affective responses triggered by illness on health outcomes [58,92], although the investigation of their predictive role on post-surgical pain has been scarce [78,80]. Post-surgical anxiety is such a response, present findings highlighting the need to address anxiety throughout the perioperative period, and not only before surgery.

While all baseline psychological factors are common predictive factors for both PT2 and PT3 membership, pre-surgical fear of long-term consequences of surgery was the only variable specifically distinguishing these groups. Hence, presenting higher levels of fear related with long-term issues, such as fear of health deterioration or long-lasting surgical recovery, appears to confer a greater risk of long-lasting pain.

The set of predictive models used in this study, which include pre- and perioperative emotion and cognitions, seem to reveal a psychological vulnerability profile, influencing post-surgical pain trajectory and ultimately the development of CPSP. This critical role of psychological factors on pain experience helps to understand the discrepancy that sometimes emerges between physical pathology, injury and pain report [16,56,87,109]. These findings are also in accordance with the gate control and neuromatrix theories of pain [65,66], as well as with the biopsychosocial approach to pain [37], which recognize pain as a multidimensional subjective experience.

Peripheral sensitization, central sensitization and descending modulation constitute three interweaved processes believed to underlie CPSP [63]. Augmented activation of pain pathways may stem from peripheral and/or central sensitization, though pain amplification may also arise from abnormalities in descending modulatory systems [73,82,111]. These descending pathways involve endogenous opioids, serotonin and noradrenaline, presenting both excitatory and inhibitory actions on spinal cord afferent projection neurons and could be activated by psychological factors [11]. Catastrophizing, anxiety, and other negative emotions are associated with reduced effectiveness in descending pain-inhibitory systems [84,106], facilitating spinal nociception and pain, whereas positive affect and self-regulatory skills inhibit spinal nociception and pain [28,39,89-91]. The primary role of catastrophizing in pain modulation has been highlighted [16,18,34,39,51,95] and suggested to be associated with diminished endogenous inhibition of pain coupled with central sensitization [84]. Moreover, an association was shown between adaptive pain coping strategies and activation of descending endogenous opioid systems [1] and between depressed mood and impaired endogenous inhibition of pain [30].

4.3. Practical and Clinical implications

Since chronic pain is very difficult to treat, the importance of secondary prevention is highlighted [38,94]. Besides, and despite the enthusiastic and promising findings of some trials focusing on preventive analgesic approaches [10,12,21,29,75,97], there is not yet any robust evidence to support the unequivocal efficacy of systemic drugs for CPSP prevention [9,17,19,43,54,61,64,87]. Moreover, notwithstanding the advances in knowledge about pain genetics [22,31,32,71,72], there is not, until now, sustained evidence for genetic predisposition for CPSP development [22,49,68,87] that could assist in screening for pain-prone patients and in informing a personalized pain treatment protocol. This leaves room for the implementation of psychological interventions aimed at preventing CPSP [15,23,33,48-50,63,100]. Indeed, present findings point to CPSP predictors that are modifiable risk factors, amenable to change or to active management, precisely through psychological interventions. Targeting them might yield adaptive and functional changes in brain pain processing, thus being an effective way to prevent CPSP development [34,95].

The effectiveness of psychological interventions in pain is well established [36,46], though in the surgical field it is overdue [15,48,56]. As substantial advances are being made in identifying risk factors for CPSP, the design and testing of preventive pain-management strategies stemming from this evidence is warranted as well as the analysis of their cost-effectiveness. An enthusiastic and promising novelty in this field is the development and implementation of a Transitional Pain Service, a multidisciplinary program aimed at preventing and managing CPSP, which offers simultaneous psychological and pharmacological interventions [20,23,42,50].

Psychological interventions have the power to impact supraspinal mechanisms involving higher pain centers [63], influencing endogenous modulation of pain, thereby improving endogenous analgesia, similarly to mechanisms underlying pharmacological analgesia [34,45,46,84]. For example, cognitive-behavioral therapy has been related to changes in brain limbic activity, which have been implicated in improvement of anxiety and potentiation of descending modulatory inhibition of pain [55,108]. Increased grey matter in prefrontal and parietal brain regions linked with chronic pain, was also observed following cognitive-behavioral therapy, being associated with a decrease in pain catastrophizing [96].

4.4. Limitations and Strengths

This is a single-site and single-country study, which compromises its external validity, thus limiting the generalization of results. Sample attrition is a potential limitation, stemming from the longitudinal design, although our study showed high retention over time. Other potential limitation is the absence of a physical examination at T3 and T4, screening for inflammation or nerve injury.

The breath of pre-surgical measures, embracing demographic, clinical and a thorough range of psychological variables was a strength, along with the long-term follow-up of 5 years.

4.5. Conclusion

This study identified risk factors that can be easily screened before and after surgery, and are amenable to intervention. The design of timely and tailored interventions for women at risk of an unfavorable post-surgical pain trajectory after hysterectomy is a key priority. Incorporating risk-targeted multidisciplinary and feasible interventions focused on CPSP prevention into surgical routine practice is an important challenge that is likely to contribute to the improvement of pain management and patient care throughout the process of surgery.

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Conflict of Interest statement

We declare that none of the authors have any financial or other relationships that might lead to conflict of interest.

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Figure 1: Flowchart of Women undergoing Hysterectomy

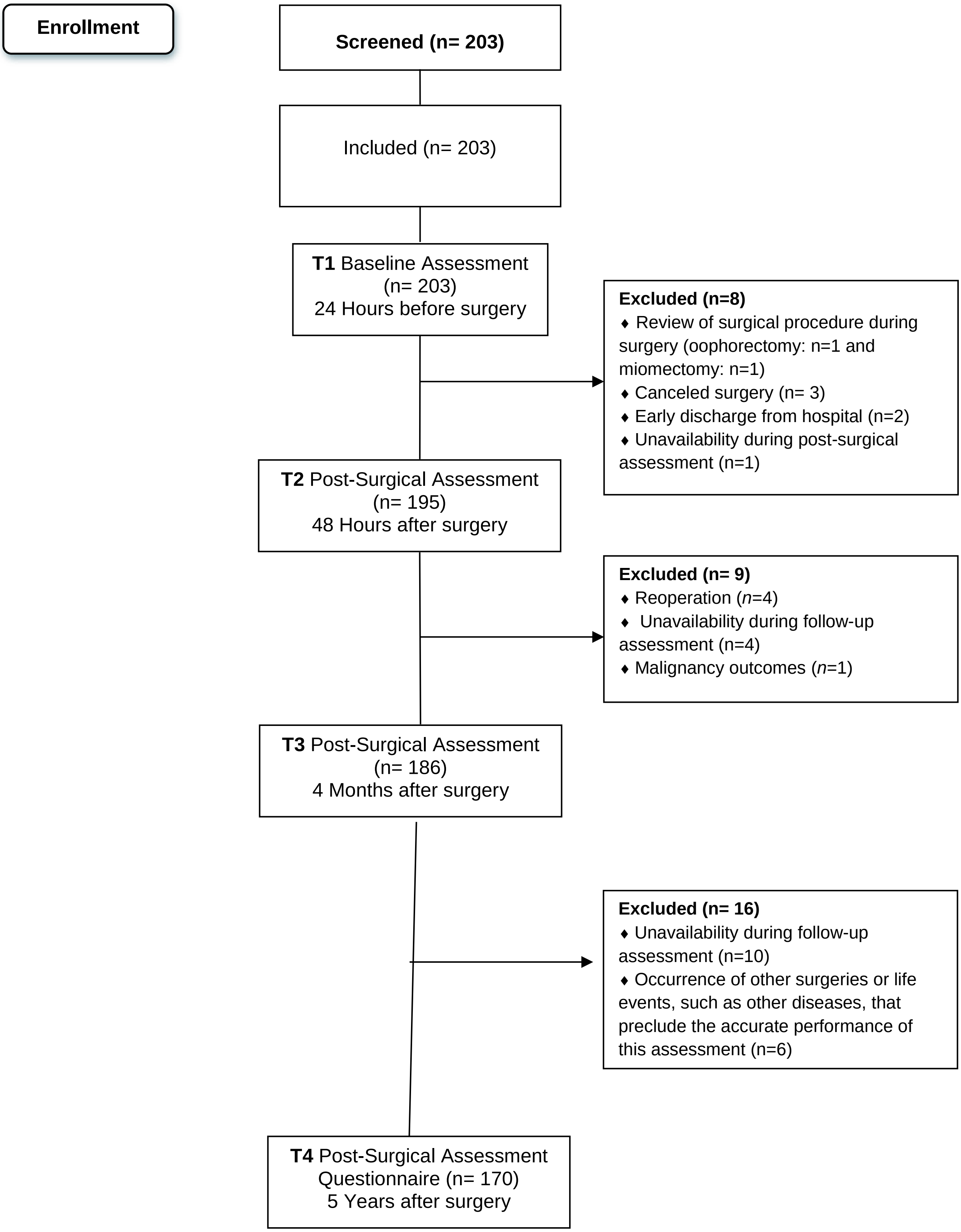

Table 1

Pain trajectory groups according to pain report at 4 months (T3) and 5 years (T4) after hysterectomy

Pain Trajectories	CHRONIC PAIN REPORT (*N*=170)			Group Designation
	T3 (4 Months after surgery)	**T4** (5 Years after surgery)	*n* (%)	
Pain Trajectory 1 (PT1)	NO	NO	88 (51.8%)	No Chronic Post-Surgical Pain
Pain Trajectory 2 (PT2)	YES	NO	53 (31.2%)	Prolonged Post-Surgical Pain
Pain Trajectory 3 (PT3)	YES	YES	29 (17.1%)	Chronic Post-Surgical Pain

Table 2

Differences between pain trajectory groups on socio-demographic, clinical and psychological variables measured 24 hours before (T1) and 48 hours after Hysterectomy (T2)

MEASURES	Pain Trajectory 1 (PT1) (*n* = 88)	Pain Trajectory 2 (PT2) (*n*= 53)	Pain Trajectory 3 (PT3) (*n*= 29)	F / χ^2	*p*	η^2 / φ
Pre-surgical data 24H before surgery-T1						
SOCIO-DEMOGRAPHIC: Age [years(*SD*)]	52.8 (10.2)[a]	48.7 (6.43)[b]	48.7 (8.19)[ab]	4.446	**0.013**	**0.051**
PRE-SURGICAL CLINICAL VARIABLES						
Disease onset (months)	39.2 (48.6)	36.3 (46.0)	44.9 (71.4)	0.250	0.779	0.003
BMI[1] (Kg/m2)	28.8 (4.26)	29.0 (4.78)	27.9 (4.15)	0.585	0.558	0.007
Previous surgeries (yes)	62 (70.5%)	37 (69.8%)	21 (72.4%)	0.063	0.969	0.019
Psychotropic use[2] (yes)	28 (33.7%)	19 (37.3%)	14 (48.3%)	1.941	0.379	0.109
Pre-surgical pain (yes)	44 (50.0%)	36 (67.9%)	21 (72.4%)	6.858	**0.032**	**0.201**
Previous pain due to other causes[3] (yes)	49 (55.7%)	37 (69.8%)	21 (72.4%)	4.176	0.124	0.157
PSYCHOLOGICAL VARIABLES (Range)						
HADS[4]: Anxiety (0-21)	6.02 (3.84)[b]	7.87 (3.96)[a]	9.38 (4.81)[a]	8.615	**<0.001**	**0.094**
HADS[4]: Depression (0-21)	1.89 (2.48)	2.68 (3.71)	2.69 (2.93)	1.509	0.224	0.018
SFQ[5]: Immediate consequences (0-40)	9.02 (8.55)	10.8 (7.26)	13.3 (10.1)	2.892	0.058	0.033
SFQ[5]: Long-term consequences (0-40)	4.61 (6.78)[b]	4.66 (5.33)[b]	8.41 (8.12)[a]	3.929	**0.022**	**0.045**
IPQ-R[6]: Timeline acute/chronic (3-15)	6.11 (1.39)	5.98 (1.01)	6.52 (1.53)	1.607	0.204	0.019
IPQ-R[6]: Timeline cyclical (3-15)	6.94 (3.09)	7.85 (3.20)	8.28 (3.36)	2.530	0.083	0.029
IPQ-R[6]: Treatment control (3-15)	12.2 (0.98)	12.2 (0.77)	12.1 (0.75)	0.231	0.794	0.003
IPQ-R[6]: Illness coherence (3-15)	9.27 (2.76)	9.36 (2.60)	9.90 (2.58)	0.604	0.548	0.007
IPQ-R[6]: Emotional representation (3-15)	7.60 (2.89)[b]	9.04 (2.90)[a]	9.62 (2.68)[a]	7.383	**0.001**	**0.081**
CSQ-R[7]: Pain catastrophizing (6-30)	9.25 (4.28)[b]	11.3 (5.81)[ab]	13.6 (6.50)[a]	8.232	**<0.001**	**0.090**
CSQ-R[7]: Praying /Hoping (3-15)	9.57 (4.22)	10.0 (4.04)	10.5 (3.67)	0.560	0.573	0.007
CSQ-R[7]: Ignoring (5-25)	12.4 (5.81)	11.9 (6.18)	11.0 (6.12)	0.568	0.568	0.007
CSQ-R[7]: Diverting attention (5-25)	9.70 (4.70)	10.2 (4.54)	9.86 (4.76)	0.213	0.808	0.003
CSQ-R[7]: Reinterpreting pain (4-20)	6.71 (3.23)	7.00 (3.52)	6.96 (3.88)	0.133	0.876	0.002
CSQ-R[7]: Pain coping self-stat (4-20)	16.0 (3.61)	15.9 (3.53)	14.9 (3.57)	1.092	0.338	0.014
LOT-R[8]: Optimism (0-12)	7.30 (3.48)	6.63 (3.01)	7.14 (3.25)	0.663	0.517	0.008
POST-SURGICAL VARIABLES						
Type hyst[9]: open abdominal	54 (61.4%)	43 (81.1%)	25 (86.2%)	9.978	**0.007**	**0.242**
Abdom. Incis.[10]: Pfannenstiel	42 (47.7%)	39 (73.6%)	21 (72.4%)	11.460	**0.003**	**0.260**
Uterus weight (gr)	219 (220)	217 (207)	205 (213)	0.045	0.956	0.001
Uterus height (cm)	9.61 (2.65)	9.30 (2.70)	9.49 (2.62)	0.228	0.797	0.003
Worst pain intensity[11]	4.40 (2.85)[b]	5.70 (2.79)[a]	6.86 (3.03)[a]	8.853	**<0.001**	**0.096**
Average pain intensity[11]	2.59 (1.61)[b]	3.55 (1.58)[a]	3.55 (1.43)[a]	7.901	**0.001**	**0.086**
Pain Frequency[12]: constant	17 (19.3%)	18 (34.0%)	16 (55.2%)	13.928	**0.001**	**0.286**
HADS[4]: Anxiety	2.05 (2.50)[b]	3.23 (3.83)[b]	5.21 (4.36)[a]	10.18	**<0.001**	**0.109**
Psychotropic use[2] (yes)	33 (37.5%)	21 (39.6%)	14 (50%)	1.392	0.498	0.091
Length of stay (days)	3.10 (0.94)	3.00 (0.56)	3.00 (0.48)	0.373	0.689	0.005

Note: Continuous variables are presented as Mean (Standard deviation); Categorical variables are presented as *n* (%);[1]BMI = body mass index; [2]Psychotropic use: Consumption / Intake of anxiolytics and anti-depressants; [3]Other previous chronic pain states not related to the cause of surgery; [4]HADS = Hospital Anxiety and Depression Scale; [5]SFQ = Surgical Fear Questionnaire; [6]IPQ-R= Illness Perception Questionnaire-Revised; [7]CSQ-R=Coping Strategies Questionnaire-Revised; [8]LOT-R = Life Orientation Test – revised; [9]Type of hysterectomy: n(%) of open abdominal hysterectomies vs abdominal laparoscopic, vaginal and vaginal assisted laparoscopic; [10]Abdominal incision: n(%) of pfannenstiel incisions vs infraumbilical vertical incision and laparoscopies; [11]NRS=Numerical Rating Scale 0-10 from Brief Pain Inventory (BPI); [12]Pain Frequency: constant pain vs intermittent or brief pain, assessed via frequency subscale of McGill Pain Questionnaire.

[abc]: Different letters represent *p*-values < 0.05 in ANOVA post-hoc tests; for example, in age groups comparisons PT1 (represented with [a]) is significantly different from PT2 (represented with [b]) and PT3 does not significantly differ from PT1 and PT2 (represented with [ab]).

Table 3 – Incidence, characteristics and impact of pain 5 years after Hysterectomy (*N*=29)

Pain 5 years after Hysterectomy – T4	*N* (%)	*M (SD)*	*Min-Max*
Pain Report - CPSP[1]	**29 (17.1%)**		
Frequency			
Daily	7 (24.2%)		
Several times a week but not daily	13 (44.8%)		
Several times a month but not weekly	3 (10.3%)		
During sexual intercourse / by touch	6 (20.7%)		
Intensity[2] (NRS 0-10)			
Worst level		3.17 (1.61)	1 - 7
NRS>3	10 (34.5%)		
Average level		1.89 (0.88)	1 - 4
NRS>3	1 (3.4%)		
DN-4[3] (Could report one or more)			
Pins and Needles	15 (51.7%)		
Numbness	9 (31.0%)		
Itching	6 (20.7%)		
Tingling	3 (10.3%)		
Burning	2 (6.9%)		
Painful cold	1 (3.4%)		
Electric shocks	1 (3.4%)		
DN4<3	23 (82.8%)		
DN4≥3	5 (17.2%)		
Pain Interference[4] (NRS 0-10)			
General activity	12 (42.9%)	1.07 (1.41)	0 - 4
Mood	16 (57.1%)	1.64 (1.83)	0 - 5
Walking Ability	8 (28.6%)	0.57 (1.03)	0 – 3
Normal Work	12 (42.9%)	1.14 (1.56)	0 – 5
Relations with other people	5 (17.8%)	0.32 (0.77)	0 – 3
Sleep	2 (7.2%)	1.79 (0.67)	0 – 3
Enjoyment of life	14 (50%)	1.32 (1.68)	0 - 5

Note: Continuous variables are presented as mean (standard deviation); categorical variables are presented as *n* (%); [1]Women reporting CPSP - chronic post-surgical pain 5 years after hysterectomy; [2]NRS: Numerical Rating Scale (0 - 10); [3]DN-4: Neuropathic Pain Questionnaire; [4]Items from BPI-SF: Brief Pain Inventory – short form.

Table 4

Multinomial logistic regression model relating Pain Trajectory Membership with pre-surgical variables measured 24 hours before Hysterectomy

Pain Trajectory Comparison	PRE-SURGICAL MODELS	Nagelkerke R^2	B	SE	Wald	OR	95% CI LL	95% CI UL
	MODEL 1A – Emotional Distress	0.206						
PT1 VS PT2	Age[1]		-0.036	0.024	2.334	0.964	0.920	1.010
	Pre-surgical pain[2]		0.231	0.416	0.309	1.260	0.557	2.851
	Type of Hysterectomy[3]		0.750	0.447	2.820	2.118	0.882	5.084
	Pre-surgical anxiety[a]		0.123	0.051	5.924*	**1.131**	1.024	1.249
	Pre-surgical fear[b]		-0.044	0.034	1.677	0.957	0.895	1.023
PT1 VS PT3	Age[1]		-0.013	0.032	0.157	0.987	0.927	1.052
	Pre-surgical pain[2]		0.706	0.534	1.752	2.026	0.712	5.767
	Type of Hysterectomy[3]		1.010	0.621	2.650	2.747	0.814	9.273
	Pre-surgical anxiety[a]		0.161	0.062	6.799**	**1.175**	1.041	1.326
	Pre-surgical fear[b]		0.031	0.035	0.802	1.032	0.964	1.104
PT2 VS PT3	Age[1]		0.024	0.034	0.471	1.024	0.957	1.095
	Pre-surgical pain[2]		0.475	0.557	0.726	1.608	0.540	4.790
	Type of Hysterectomy[3]		0.260	0.669	0.151	1.297	0.350	4.809
	Pre-surgical anxiety[a]		0.038	0.062	0.376	1.039	0.920	1.173
	Pre-surgical fear[b]		0.075	0.038	3.880*	**1.078**	1.000	1.162
	MODEL 1B[a] - Illness Perceptions	0.171						
PT1 VS PT2	Age[1]		-0.030	0.023	1.697	0.970	0.928	1.015
	Pre-surgical pain[2]		0.263	0.405	0.423	1.301	0.588	2.878
	Type of Hysterectomy[3]		0.793	0.445	3.168	2.209	0.923	5.290
	Emotional representation[c]		0.152	0.064	5.586*	**1.165**	1.026	1.321
PT1 VS PT3	Age[1]		-0.018	0.030	0.378	0.982	0.926	1.041
	Pre-surgical pain[2]		0.430	0.515	0.698	1.538	0.560	4.219
	Type of Hysterectomy[3]		1.166	0.621	3.530	3.209	0.951	10.829
	Emotional representation[c]		0.220	0.079	7.821**	**1.246**	1.068	1.455
	MODEL 1C[a] – Pain Coping Strategies	0.178						
PT1 VS PT2	Age[1]		-0.037	0.023	2.611	0.963	0.921	1.008
	Pre-surgical pain[2]		0.373	0.402	0.862	1.452	0.661	3.190
	Type of Hysterectomy[3]		0.609	0.045	1.878	1.839	0.769	4.395
	Pain catastrophizing[d]		0.076	0.038	4.086*	**1.079**	1.002	1.162
PT1 VS PT3	Age[1]		-0.034	0.031	1.172	0.967	0.910	1.028
	Pre-surgical pain[2]		0.577	0.520	1.231	1.781	0.642	4.940
	Type of Hysterectomy[3]		0.798	0.623	1.641	2.221	0.655	7.532
	Pain catastrophizing[d]		0.134	0.042	10.170***	**1.143**	1.053	1.241

*p<0.05; **p<0.01; ***p<0.001

Note: PT1: Pain Trajectory Group 1 (No Chronic Post-Surgical Pain); PT2: Pain Trajectory Group 2 (Prolonged Post-Surgical Pain); PT3: Pain Trajectory Group 3 (Chronic Post-Surgical Pain). [1]Continuous variable, in years; [2]Dichotomous variable: 0= No, 1= Yes; [3]Dichotomous variable: 0= abdominal laparoscopic, vaginal and vaginal assisted laparoscopic; 1= open abdominal hysterectomies; [a]Continuous variable, HADS-A: Hospital Anxiety and Depression Scale - anxiety subscale; [b]Continuous variable, Surgical Fear Questionnaire – fear of immediate consequences of surgery subscale; [c]Continuous variable, IPQ-R: Illness Perception Questionnaire Revised – all subscales; [d]CSQ-R: Coping Strategies Questionnaire Revised – all subscales.

PT1 - Reference Group (In MODEL 1A PT2 VS PT3, PT2 is the reference group); OR - Odds Ratio; LL - Lower Limit; UL - Upper Limit.
[a]For models 1B and 1C, no significant predictors were found in the comparison of PT2 and PT3.

Table 5

Multinomial logistic regression model relating Pain Trajectory Membership with post-surgical variables measured 48 hours after Hysterectomy

Pain Trajectory Comparison	POST-SURGICAL MODELS	Nagelkerke R^2	B	SE	Wald	OR	95% CI LL	95% CI UL
	MODEL 2A[a] – Acute Pain	0.192						
PT1 VS PT2	Age		-0.031	0.023	1.774	0.970	0.927	1.015
	Pre-surgical pain[2]		0.289	0.404	0.511	1.335	0.605	2.946
	Type of Hysterectomy[3]		0.640	0.443	2.083	1.896	0.795	4.552
	Acute post-surgical pain intensity[4]		0.067	0.069	0.957	1.070	0.935	1.224
	Acute post-surgical pain frequency[5]		0.429	0.431	0.992	1.535	0.660	3.571
PT1 VS PT3	Age		-0.011	0.032	0.114	0.989	0.929	1.053
	Pre-surgical pain[2]		0.388	0.527	0.543	1.474	0.525	4.139
	Type of Hysterectomy[3]		0.765	0.634	1.457	2.149	0.620	7.441
	Acute post-surgical pain intensity[4]		0.191	0.090	4.525*	**1.211**	1.015	1.444
	Acute post-surgical pain frequency[5]		1.099	0.505	4.741*	**3.000**	1.116	8.065
	MODEL 2B[a] – Acute Pain + Anxiety	0.222						
PT1 VS PT2	Age[1]		-0.031	0.023	1.743	0.970	0.926	1.015
	Pre-surgical pain[2]		0.360	0.410	0.771	1.433	0.642	3.201
	Type of Hysterectomy[3]		0.637	0.446	2.041	1.890	0.789	4.527
	Acute post-surgical pain intensity[4]		0.031	0.074	0.172	1.031	0.892	1.192
	Acute post-surgical pain frequency[5]		0.306	0.445	0.474	1.358	0.568	3.250
	Post-surgical anxiety[a]		0.093	0.068	1.863	1.098	0.960	1.255
PT1 VS PT3	Age[1]		-0.016	0.033	0.234	0.984	0.923	1.050
	Pre-surgical pain[2]		0.430	0.536	0.643	1.537	0.538	4.391
	Type of Hysterectomy[3]		0.715	0.646	1.224	2.044	0.576	7.255
	Acute post-surgical pain intensity[4]		0.123	0.097	1.620	1.131	0.936	1.367
	Acute post-surgical pain frequency[5]		0.786	0.536	2.152	2.195	0.768	6.277
	Post-surgical anxiety[a]		0.167	0.075	4.945*	**1.182**	1.020	1.370

*p<0.05; **p<0.01; ***p<0.001

Note: PT1: Pain Trajectory Group 1 (No Chronic Post-Surgical Pain); PT2: Pain Trajectory Group 2 (Prolonged Post-Surgical Pain); PT3: Pain Trajectory Group 3 (Chronic Post-Surgical Pain). [1]Continuous variable, in years; [2]Dichotomous variable: 0= No, 1= Yes; [3]Dichotomous variable: 0= abdominal laparoscopic, vaginal and vaginal assisted laparoscopic; 1= open abdominal hysterectomies; [4]Continuous variable, NRS 0-10 from BPI-SF: Brief Pain Inventory-Short Form; [5]Dichotomous variable: 0= intermittent or brief pain, 1=constant pain, frequency subscale of McGill Pain Questionnaire; [a]Continuous variable, HADS-A: Hospital Anxiety and Depression Scale - anxiety subscale;

PT1 - Reference Group; OR - Odds Ratio; LL - Lower Limit; UL - Upper Limit.

[a] For models 2A and 2B, no significant predictors were found in the comparison of PT2 and PT3.